DISSERTATION ON

”EVALUATING THE EFFICACY OF INJ.METOPROLOL 50µgm/ Kg.I.V., IN ATTENUATING HEMODYNAMIC RESPONSE TO LARYNGOSCOPY, INTUBATION AND CARBON DIOXIDE PNEUMOPERITONEUM IN PATIENTS UNDERGOING LAPAROSCOPIC APPENDICECTOMY.”

**Submitted to**

**THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY**

**In partial fulfillment of the requirement**

**For the award of degree of**

**M.D. BRANCH X**

**(ANAESTHESIOLOGY)**

**DEPARTMENT OF ANAESTHESIOLOGY**

**STANLEY MEDICAL COLLEGE**

**THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY**

**CHENNAI**

**March 2009**

## CERTIFICATE

This is to certify that this dissertation entitled "**EVALUATING THE EFFICACY OF Inj.METOPROLOL 50µgm./Kg.I.V., IN ATTENUATING HEMODYNAMIC RESPONSE TO LARYNGOSCOPY, INTUBATION AND CARBON DIOXIDE PNEUMOPERITONEUM IN PATIENTS UNDERGOING LAPAROSCOPIC APPENDICECTOMY**." is a bonafide record work done by Dr. N.V.MADHAVAKRISHNA under my guidance and supervision, in the Department of Anaesthesiology, Government Stanley Medical College, in partial fulfillment of the requirement for MD anaesthesiology examination of the TamilNadu Dr. MGR Medical University to be held in March 2009.

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# DECLARATION

I, Dr.N.V. MADHAVAKRISHNA, solemnly declare that dissertation titled, ”evaluating the efficacy of inj.metoprolol 50micrograms/kg.i.v., in attenuating hemodynamic response to laryngoscopy, intubation and carbon dioxide pneumoperitoneum in patients undergoing laparoscopic appendicectomy.” is the bonafide work done by me at Govt.Stanley medical college and hospital during the period January 2008 to August 2008 under the expert guidance and supervision of Prof. Dr. P. Chandrasekar M.D. D.A.

The dissertation is submitted to the Tamilnadu Dr. MGR Medical university towards partial fulfillment of requirement for the award of MD Degree in anaesthesiology.

Place :

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## ACKNOWLEDGEMENT

I wish to express my sincere thanks to **Prof. Dr. J. MOHANASUNDARAM** , **MD., D.N.B., Ph.D., DEAN**, Govt. Stanley Medical College and Hospital for having kindly permitted me to utilize the facilities of the hospital for the conduct of the study.

I thank the Hospital Ethical Committee, for granting me permission to conduct the study.

My heartfelt thanks to **PROF. DR.P.CHANDRASEKAR., M.D. D.A., Prof.& HOD,** Department of Anaesthesiology, Govt. Stanley Medical College and Hospital for his motivation, valuable suggestions, constant supervision and for providing all necessary arrangements for conducting the study.

I am greatly indebted to **Prof. Dr. B. KALA, M.D.D.A., Prof.Dr. R. MADHAN KUMAR, M.D.D.A., Prof. Dr. S. GUNASEKARAN, M.D., D.A.,** for their expert guidance during the study.

I Express my gratitude, to **Dr. Satish Logidasan M.D.D.A.,** Assistant Professor, for his constant guidance, supervision and support in all aspects in conducting this study.

I owe a lot to Assistant Professors **Dr.Saravanakumar M.D.D.A.,Dr. V.J. Karthik M.D.D.A., Dr. Narasimhan M.D.D.A., Dr. Gomathikarmegam M.D.D.A., Dr. Deepthi M.D.D.A.,** who were guiding me throughout the study and supervising periodically.

I thank **ALL ASSISTANT PROFESSORS** who evinced keen interest and gave support without which this study would not have been possible.

I thank **Mr. Padmanaban,** Statistician, for helping me in the statistical analysis.

I thank all the post graduates for their valuable support during the study period. I thank all the theatre personnel for their co-operation.

And last but not the least my sincere thanks to all the 60 patients, without whom this study would not have been possible.

# ”EVALUATING THE EFFICACY OF INJ.METOPROLOL 50µgm./Kg.I.V., IN ATTENUATING HEMODYNAMIC RESPONSE TO LARYNGOSCOPY, INTUBATION AND CARBON DIOXIDE PNEUMOPERITONEUM IN PATIENTS UNDERGOING LAPAROSCOPIC APPENDICECTOMY.”

# CONTENTS

# INTRODUCTION

Laryngoscopy and intubation cause a marked increase in adrenergic activity due to stress response. The resulting tachycardia, hypertension and arrhythmias may cause hemodynamic instability in patients with cardiovascular disease.

Laparoscopic procedures for both diagnostic and surgical purposes are becoming increasingly popular. They offer specific advantages to the patient like, less post operative pain[35,27], less severe respiratory dysfunction and quicker recovery[13,41],less tissue damage and inflammation[13,10],nitrogen balance and immune function are better preserved[5], shorter hospital stay, early ambulation, less morbidity and smaller scars. Carbon dioxide pneumoperitoneum produced during these procedures causes similar hemodynamic changes as in airway manipulation. This may be due to[44],

Increased intra abdominal pressure,
Neurohumeral responses and
Absorbed carbon dioxide leading to hypercarbia

Much of the initiation of the stress response relies on the outflow of the sympathetic neuronal pathway. Many pharmacological techniques using

adrenoreceptor blockers, calcium channel blockers, opioids, vasodilators were used to attenuate these responses, which indicates lack of an ideal drug for this purpose.

Metoprolol, a selective $\beta_1$ adrenergic blocking agent acts by,
competitive antagonism of catecholamines at peripheral(especially cardiac) adrenergic neuron sites, leading to decreased blood pressure;
Central effect leading to reduced sympathetic outflow to the periphery;
Suppression of renin activity.

These properties of metoprolol make it suitable for suppressing the stress response. Moreover, the elimination halftime of Metoprolol[43] being 3.5 hours allows it to be administered as a single dose covering the duration of surgery. Thus in this study we are evaluating the efficacy of injection metoprolol 50 micrograms/ kg. i.v., in attenuating these stress responses.

# AIM OF THE STUDY

1. To study the efficacy of Inj.Metoprolol 50 micrograms/kg i.v. given 5 minutes before induction of anesthesia in attenuating hemodynamic stress response to laryngoscopy, intubation and carbon dioxide pneumoperitoneum in laparoscopic appendicectomies.

2. To observe for any complications related to inj.Metoprolol during intra operative period and 8 hours postoperatively.

# SYMPATHETIC RESPONSE TO LARYNGOSCOPY

Laryngoscopy and intubation produces a cardiovascular stress response. The Cardiovascular changes during laryngoscopy and endotracheal intubation are

Hypertension,

Tachycardia and

Dysrrhythmias.

The body reacts to external stimuli, ranging from minor to massive insult both locally and generally. The general response is in the form of wide spread endocrinal, metabolic and biochemical reactions throughout the body. The magnitude of the response is highly dependent on severity, intensity and duration of the stimulus. For triggering such reflex response and presenting a complex interplay of substances between the hypothalamic pituitary axis, the classical neuro-endocrine hormone system and autonomic nervous system is brought to action and is called "stress response[2]"

During laryngoscopy and intubation the mechanical stimulation of upper respiratory tract viz nose, epipharynx, laryngopharynx, the afferents are carried by glossopharyngeal nerve: from tracheobronchial tree via vagus nerve which enhances the activities of the cervical sympathetic afferent fibres resulting in transient rise in heart rate and blood pressure[24]. There is increase in plasma epinephrine, norepinephrine and vasopressin concentrations during laryngoscopy and intubation[14].

In healthy patients these responses are well tolerated. However, in patients with limited coronary or myocardial reserve, myocardial ischemia or failure may follow.

Because the MAC for endotracheal intubation is about 30 percent higher than MAC for surgical incision[44], a relatively deep level of anesthesia must be established to blunt these responses. Deeper anesthesia may not be well tolerated by many patients. So drugs that tend to block the response to airway instrumentation or antihypertensives can be used.

Opioids such as Fentanyl, Alfentanyl and Remifentanyl are an option for blunting the stress response to intubation.

Lignocaine in a dose of 1.5mg/kg. intravenously is also used to blunt this response. Topical anesthesia with lignocaine is a less effective method for

blunting the hemodynamic responses to laryngoscopy because laryngoscopy precedes intra tracheal administration of lignocaine. Transtracheal injection of local anaesthetic avoids laryngoscopy but it is stimulating in its own right. Glossopharyngeal and superior laryngeal nerve blocks may also be effective methods to blunt the hemodynamic response to laryngoscopy.

A variety of antihypertensive agents have also been used to diminish the hemodynamic responses to intubation. These include ß adrenergic blockers like esmolol,metoprolol and propranolol;,Phentolamine,Nitroprusside,Nitroglycerine, Clonidine and Hydralazine, all have their own advocates.

# HEMODYNAMIC ALTERATIONS DUE TO $CO_2$ PNEUMOPERITONEUM

## Hemodynamic Repercussions In Healthy Patients

Peritoneal insufflation to intra abdominal pressures higher than 12 mm of Hg. induces significant alterations of hemodynamics. They are ,

Elevations of Arterial Pressure

Increase in Heart Rate

Increase in Systemic and Pulmonary Vascular Pressures

Decrease in Cardiac Output

These adverse hemodynamic effects of pneumoperitoneum have been confirmed by studies using pulmonary artery catheterisation[8], thoracic electrical bio impedance[42], esophageal echo-doppler[31],and tran sesophageal echocardiography[26].

The mechanism of decrease in cardiac output is probably multi factorial, decrease in venous return being the most important. Cardiac filling pressures however rise during peritoneal insufflations. The paradoxic increase in these

pressures can be explained by the increased intra thoracic pressure associated with pneumoperitoneum. The reduction in venous return and cardiac output can be attenuated by increasing the circulating volume before the pneumoperitoneum by fluid loading[44].

Increase in Systemic Vascular Resistance during pneumoperitoneum cannot be considered simply to be a reflex sympathetic response to decreased cardiac output. Indeed Systemic Vascular resistance also increased in studies in which no decrease in cardiac output was reported[32]. The increase in systemic vascular resistance is considered to be mediated by mechanical as well as neurohumoral factors[41]. Indeed, the return of hemodynamic variables to baseline is gradual and takes several minutes suggesting neurohumoral factors[38,41]. Catecholamines, the renin angiotensin system and vasopressin released during pneumoperitoneum may contribute to increasing afterload[8,42]. Mechanical stimulation of peritoneal receptors also results in increased vasopressin release[28],systemic vascular resistance and arterial pressure[21].

Urine output, renal plasma flow and glomerular filtration rate decrease to less than 50 percent of baseline values during laparoscopic surgeries than during open surgeries[9]. Urine output significantly increases after desufflation.

## Hemodynamic Repercussions Of Pneumoperitoneum In High Risk Cardiac Patients

In patients with mild to severe cardiac disease, the pattern of change in mean arterial pressure, cardiac output and systemic vascular resistance is qualitatively similar to that in healthy patients[34,36]. Quantitatively these changes seem to be more marked, putting these patients at increased risk of developing congestive cardiac failure.

## Cardiac Arhythmias During Laparoscopy

Arrhythmias during laparoscopy may have several causes. Hypercapnia is blamed more often. But, arrhythmias are not correlated with PaCO2 and may develop during insufflation, when high PaCO2 is unikely. Reflex increases in vagal tone may result from sudden stretching of the peritoneum. Bradycardia,

cardiac arrhythmias and even asystole can develop. Gas embolism can also result in cardiac arrhythmias[44].

Cardiac irregularities most often occur early during insufflation, when pathophysiologic hemodynamic changes are most intense[20]. For this reason, arrhythmias may also reflect intolerance of these hemodynamic disturbances in patients with known or latent cardiac disease.

# HEMODYNAMIC ALTERATIONS DUE TO POSITIONING AND VENTILATORY CHANGES DURING LAPAROSCOPIC SURGERIES

## HEMODYNAMIC EFFECTS OF POSITIONING

Laparoscopic surgeries may require steep head up or head down tilt. Head down position results in increase in central venous pressure and cardiac output. These changes are greater with coronary artery disease patients, especially with poor ventricular function, leading to potentially deleterious, increased myocardial oxygen demand.

In head up position, a decrease in cardiac output and mean arterial pressure is observed secondary to reduction in venous return[32,8]. This decrease in cardiac output compounds the hemodynamic changes induced by pneumoperitoneum.

Venous stasis occurs in the leg during head up position. Pneumoperitoneum further increases the venous pooling in the leg.

## RESPIRATORY CHANGES DURING LAPAROSCOPIC SURGERIES

$PaCO_2$ progressively increases to reach a plateau 15 to 30 minutes after the beginning of $CO_2$ insufflation in patients under controlled mechanical ventilation in either trendelenberg position[38] or head up position[4]. This hypercarbia contributes to the Heart Rate and Blood Pressure response during laparoscopic surgeries. Causes of increased $PaCO_2$ during laparoscopy are

$CO_2$ absorption from peritoneal cavity

V/Q mismatch due to abdominal distension and position of the patient

Increased metabolism

Decreased thoracopulmonary compliance[6,7,33].

Depression of ventilation by anaesthetics(spontaneously breathing)

Accidental events $CO_2$ emphysema, Capnothorax, $CO_2$ embolism

Various methods and pharmacological agents are being used to overcome the adverse hemodynamic effects of the pneumoperitoneum. Some of them are,

Preoperative preload augmentation to offset the reduced venous return and cardiac output.
Vasodilators like Nitroglycerin to correct the reduction in cardiac output associated with increased pulmonary capillary occlusion pressures and systemic vascular resistance.
Calcium channel blockers like Nicardipine acts selectively on arterial resistance vessels and reduces systemic vascular resistance without compromising venous return[34].
ß adrenergic blockers
$\alpha_2$ adrenergic agonists such as clonidine or dexmedetomidine significantly reduce both hemodynamic changes and anaesthetic requirements[1].

# ADRENERGIC RESPONSES MEDIATED THROUGH

# αAND ß RECEPTORS

| S.No | α actions | ß actions |
|---|---|---|
| 1. | Constriction of arterioles and veins→increase in BP(mainly $\alpha_1$) | Dilatation of arterioles and veins→fall in BP($ß_2$) |
| 2. | Heart-little action,arrhythmias at high dose($\alpha_1$) | Cardiac stimulation($ß_1$),increased rate,force and conduction velocity |
| 3. | - | Bronchodilatation($ß_2$) |
| 4. | Contraction of radial muscles of iris→mydriasis($\alpha_1$)decreased aqueous secretion | No effect on iris and ciliary muscle. Enhanced aqueous secretion |
| 5. | Intestinal relaxation, Contraction of sphincters. | Intestinal relaxation($ß_2$) |
| 6. | Bladder trigone-contraction | Detrusor-relaxation |
| 7. | Splenic capsule contraction | Relaxation(slight)($ß_2$) |
| 8. | Uterus-contraction | Relaxation($ß_2$) |
| 9. | Neuro muscular transmission facilitated,Increased Ach. Release | Active state-prolonged in fast contracting muscle.abbreviated in slow contracting muscle;tremors($ß_2$) |
| 10. | Insulin secretion inhibited(dominant)($\alpha_2$) | Augmented insulin(mild) and glucogon secretion($ß_2$) |
| 11. | Liver-glycogenolysis(α in some species) | Liver-glycogenolysis($ß_2$) →hyperglycemia Muscle-glycogenolysis,$ß_2$→hyperlactacidemia Fat-lipolysis($ß_3$) →increased blood FFA,calorigenesis. |
| 12. | - | Renin release from kidney($ß_1$) |
| 13. | Salivary gland-pottasium and water secretion($\alpha_1$) | Ptylin secretion |
| 14. | - | ADH secretion from posterior pituitaryß $_1$) |

Among the ß receptors $ß_1$ receptors are located in heart and JuxtaGlomerular cells in kidney; $ß_2$ receptors are located in bronchi,blood vessels,uterus,gastrointestinal tract and eye; $ß_3$ receptors are located in adipose tissue.

# PHARMACOLOGY OF METOPROLOL

Metoprolol tartrate , is a selective $ß_1$-adrenoreceptor blocking agent, available as 50- and 100-mg tablets for oral administration and in 5-mL ampoules for intravenous administration. Each ampoule contains a sterile solution of metoprolol tartrate , 5 mg, and sodium chloride , 45 mg, and water for injection.

**Metoprolol tartrate is (±)-1-(Isopropylamino)-3-**

**[ p(2methoxyethyl)phenoxy]-2-propanol L-(+)- tartrate (2:1) salt is** and its structural formula is

Physical properties

Metoprolol has a very low melting point. Its melting point is around 45 degrees Celsius (as determined by Differential scanning calorimetry). For this reason metoprolol is always manufactured in salt form, as drugs with melting points below 100 degrees Celsius are difficult to work with in a manufacturing environment. The free base exists as a waxy white solid, where the tartrate salt is finer crystalline material

## MECHANISM OF ACTION

Metoprolol's mechanism of action :

1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decrease in blood pressure;

(2) a central effect leading to reducd sympathetic outflow to the periphery; and

(3) suppression of renin activity

## PHARMACO DYNAMICS

- Cardioselective
- Moderately Lipophilic
- Without intrinsic sympathomimetic activity (ISA)
- With weak membrane stabilizing activity
- Short half-life (t1/2 is 3.5 hours.), therefore must be taken at least twice daily or as a single dose Slow-release preparation.
- Decreases Heart Rate, Contractility and Cardiac Output, therefore decreasing blood pressure.
-

- **Metoprolol reduces or inhibits the agonistic effects on the heart of catecholamines(which are released during periods of physical or mental stress). This means that the usual increase in heart rate, contractility and blood pressure, produced by acute increases in catecholamines is decreased by metoprolol**.
- When given together with a $ß_2$ agonist, metoprolol in therapeutic doses interferes less than nonselective ß blockers with the $ß_2$ mediated bronchodilatation produced by the $ß_2$ agonist. When mandatorily required it can be given to patients with obstructive pulmonary disease along with a $ß_2$ agonist.
- Metoprolol interferes less with insulin release and carbohydrate metabolism than do non selective ß blockers.
- Interferes much less with cardiovascular response to hypoglycemia than do non selective ß blockers.
- Metoprolol may cause a slight increase in triglycerides, decrease in free fatty acids, small decrease in the High Density Lipoproteins.

## PHARMACO KINETICS

### Absorption and Distribution

After i.v. injection, metoprolol is rapidly distributed in the initial 5minutes to 10 minutes.After oral administration completely absorbed. Peak plasma concentrations obtained after 1.5 to 2 hours. Owing to extensive first-pass effect, bio availability of metoprolol after oral dose is 50 to 70 percent. The plasma protein binding of metoprolol is low, 5 to 10 percent.

### Metabolism and Elimination[43]

Metoprolol undergoes oxidative metabolism in the liver. Three main metabolites have been identified, none of them have a ß blocking effect of clinical importance. Elimination half life of metoprolol in plasma averages 3.5 hours(extremes:1 and 9 hours). The total clearance rate is approximately 1 litre/minute.

Elderly show no significant changes in the pharmacokinetics of metoprolol as compared to the young adults.The systemic bio availability and elimination of metoprolol is unchanged in persons with reduced renal function.Due to its low protein binding the pharmacokinetics of metoprolol is little affected by decreased liver function. However, in patients with

severe cirrhosis and portacaval shunt the bio availability of metoprolol may increase and the total clearance may be reduced.

## INDICATIONS

**Usual indications of metoprolol are**:
Disturbances of cardiac rhythm especially supraventricular tachycardia.
Suspected or confirmed myocardial infarction.
Angina pectoris
Hypertension

**Dosage and Method of Administration of I.V. Metoprolol**

Initially upto 5mg injected intravenously at a rate of 1 to 2 mg per minute. The injection can be repeated at 5 minute intervals until a satisfactory response has been obtained. A total dose of 10 to 15mg generally proves sufficient. Doses of 20mg or more are unlikely to result in further therapeutic benefit.

Second or third dose should not be given if the heart rate is less than 40/minute,or if the systolic BP is less than 90 mm of Hg., or the P-Q time is more than 0.26 seconds.

Dose adjustments are not needed in elderly or persons with renal impairment. Dose adjustments is usually not needed in liver cirrhosis. But when there are signs of serious impairment of liver function or shunt operated patients a dosage reduction should be considered.

**In Pregnancy and Lactation**

Metoprolol should not be given in pregnancy and lactation unless its use is considered essential. May cause bradycardia in fetus, newborn and breast fed infant. However the amount of metoprolol ingested through breast milk seems negligible to produce significant clinical effects.

**CONTRAINDICATIONS**

Metoprolol is contraindicated in sinus bradycardia, heart block greater than first degree, significant first-degree heart block (P-R interval =0.24 sec), cardiogenic shock, and overt cardiac failure .

Hypersensitivity to Metoprolol and related derivatives, or to any of the excipients; hypersensitivity to other ß-blockers (cross sensitivity between ß-blockers can occur).

Sick-sinus syndrome.

Severe peripheral arterial circulatory disorders.

Pheochromocytoma : Should not be given without α blockade

## SPECIAL WARNINGS INTERACTION AND PRECAUTIONS

Intravenous administration of calcium antagonists should be used with caution in patients treated with ß blockers.
Patient receiving concomitant treatment with sympathetic ganglion blocking agents, other ß blockers(i.e.eye drops),or Monamine Oxidase Inhibitors should be kept under close surveillance.
Enzyme inducing and enzyme inhibiting drugs affect the plasma concentration of metoprolol. Plasma concentration of metoprolol is lowered by rifampicin and may be raised by cimetedine, alcohol and hydralazine.
Concomitant treatment with Indomethacin or other prostaglandin synthatase inhibiting drugs may decrease the antihypertensive effect of metoprolol.
In patients with Asthma concomitant treatment with ß2 agonist should be started.
In patients suffering from cardiac failure should have their decompensation treated both before and during treatment with metoprolol. If the patient develops increasing bradycardia metoprolol should be given in lower doses or gradually withdrawn.
Abrupt interruption of the medication to be avoided.

Metoprolol may aggravate the symptoms of peripheral arterial circulatory disorders.
In pheochromocytoma an α blocker should be given concomitantly.
Prior to surgery anesthetist should be informed about the metoprolol treatment. It is not recommended to stop ß blockers in patients undergoing surgery. Inhalational anesthetics enhance the cardiodepressants effect of ß blockers.

**SIDE EFFECTS OF METOPROLOL.**

Metoprolol is well tolerated and adverse reactions have generally been mild and reversible. The following events have been reported as adverse events in clinical trials or from routine use. In many cases a relationship to treatment with metoprolol has not been established.

Sys-tem
V.common
More than 10%
Common
1-9.9%
Uncommon
0.1-0.9%
Rare
0.01-o.09%
Very rare
Less than 0.01%
CVS

Bradycardia,
postural disorders,cold extremities,palpitations
Transient detoriation of heart failure,first degree block,oedema,pericardial pain
Arrhythmias,conduction disturbances
Gangrene in patients with peripheral vascular disease.
RS

Dyspnea on exertion
Bronchospasm
Rhinitis

CNS
Fatigue
Dizziness,headache
Parasthesia,muscle cramps

GIT

Nausea,abdominal pain,diarhea,
Constipation
Vomiting
Dry mouth,LFT abnormalities
Hepatitis

Thrombocytopenia, arthralgia, weight gain, depression, impaired concentration, sleep disturbances, nightmares, anxiety, sexual dysfunction, confusion, skin rash, loss of hair, photosensitivity, aggravation of psoriasis, conjunctivitis, tinnitus, taste disturbances can also occur during Metoprolol treatment.

Several cases of overdosage have been reported, some leading to death. Potential signs and symptoms associated with over dosage with metoprolol are bradycardia, hypotension, bronchospasm, and cardiac failure.

**Treatment of Metoprolol overdose[47]**

There is no specific antidote.On the basis of pharmacologic actions of Metoprolol, the following general measures should be employed

**Bradycardia:** Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

**Hypotension:** A vasopressor should be administered, e.g., norepinephrine or dopamine.

**Bronchospasm:** A ß 2-stimulating agent and/or a theophylline derivative should be administered.

**Cardiac Failure:** A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol should be considered.

Glucagon in a dose of 1 to 10mg can be administered.

Pacemaker may be necessary.

Note: Dosage of drugs needed to treat overdose of ß blockade are much higher than the normally recommended therapeutic doses. This is because ß receptors are occupied by the ß blockers

# REVIEW OF LITERATURE

In 1970 , A. Millar Forbes,M.B.,C.H.B.,F.F.A.R.C.S, and F.G.Dally M.B.B.S..M.R.A.C.G.P et al[30] studied twenty two normotensive patients , anesthesia was induced with thiopentone and suxamethonium. They found that laryngoscopy and endotracheal intubation were immediately followed by an average increase in Mean arterial pressure of 25mm of Hg.

In 1977, Lammintausta R, Syvalahti E et al[19], studied the effect of ß blockers propranolol and metoprolol on haemodynamics and plasma rennin activity of healthy volunteers in an ergometric exercise test. Oral doses of 160mg of propranolol and 200 mg of metoprolol were tested against placebo. Propranolol, but not Metoprolol decreased the basal level of Plasma rennin activity. Exercise induced significant increase in plasma rennin activity in placebo group, but this increase was partially inhibited by both the drugs. On the basis of these findings it is suggested that in man the basal level of plasma rennin activity could be decreased mainly by blocking the ß 2 adrenoreceptors. Instead exercise induced increase of plasma rennin activity could be inhibited by blocking the ß-1 adrenergic receptors.

In 1978, Stoelting R.K., et al[40], studied the changes in Mean Arterial Pressure and Heart Rate during short duration(less than 15 seconds) laryngoscopy and tracheal intubation in 24 patients undergoing elective coronary artery bypass grafting. He concluded that, laryngotracheal lidocaine administration just before tracheal intubation minimizes pressor response to intubation.
In 1986, J. Magnusson,T. Thulin, O.Werner et al[22].,studies the hemodynamic effect of pretreatment with metoprolol in patients undergoing surgery under general anesthesia with thiopentone-fentanyl-nitrous oxide-pancuronium. Patients were divided into two groups of 15. One group received metoprolol tablets 200mg in a slow release form, once daily for at least 2 weeks including the morning of surgery. In addition , metoprolol 15mg was injected i.v. shortly before induction of anesthesia. The other group received placebo tablets and saline. They concluded that metoprolol significantly reduced arterial pressure both during undisturbed anesthesia and during intubation and after extubation.
In 1991, K. Samchung M.D. of yale university, NewHayen[37] conducted a randomized double blind study to compare a combination of esmolol and fentanyl with that of either agent alone in blunting the hemodynamic response to intubation. They compared fentanyl 2 mic.gms./kg., esmolol 2mgm./kg., fentanyl 2mic.gms./kg with esmolol 2mgm./kg and fentanyl 5 mic.gms./kg. in blunting the hemodynamic response to intubation. The study concluded that combination of esmolol 2mgm/kg. with fentanyl 2 mic./kg. is better than either of them alone.

In 1992, Mikawa K, Hasegawa M, Suzuki T, Obara H et al[29] of Japan evaluated the efficacy and safety of intravenous (IV) nitroglycerin in attenuating the hypertensive response to laryngoscopy and intubation in a controlled, randomized, double-blind study. Thirty normotensive patients (ASA physical status I) undergoing elective surgery were divided into three groups of ten patients each. Anesthesia was induced with thiopental sodium 5 mg/kg i.v., and tracheal intubation was facilitated with vecuronium 0.2 mg/kg i.v. During anesthesia, ventilation was assisted or controlled with 1% enflurane and 50% nitrous oxide in oxygen. Either 1.5 micrograms/kg of nitroglycerin, 2.5 micrograms/kg of nitroglycerin, or saline (control) was administered IV simultaneously with the start of laryngoscopy (lasting 30 seconds), which was attempted 2 minutes after

administration of thiopental sodium and vecuronium. Patients receiving saline showed a significant increase in mean arterial pressure and rate-pressure product associated with tracheal intubation. These increases following tracheal intubation were significantly reduced in nitroglycerin-treated patients compared with those in the control group

In 1995. Kumar M., Tikkle AC[17] conducted a study in 60 randomly selected normotensive patients(ASA I and II) of age 20 years and above. Patients were divided into two groups of 30 each. Group 1 was the control group and received normal saline as placebo 5 minutes before induction; group 2 patients received **i.v. Metoprolol** 3 mg. 5 minutes before induction of anaesthesia. All patients were anaesthetized by thiopentone and pancuronium and intubated. It was observed that Metoprolol given 5 minutes before induction of anaesthesia effectively attenuated the cardiovascular response to laryngoscopy and endotracheal intubation to clinically significant levels.

In 1997 Walder AD, Aitkenhead AR et al[42], in a study of patients undergoing laparoscopic cholecystectomy measured heart rate, arterial pressure, right atrial pressure, cardiac index, catecholamines and vasopressin, and noticed increase in plasma vasopressin concentration after insufflations of the pneumoperitoneum to a level sufficient to cause the recorded haemodynamic changes(increase in arterial pressure, systemic vascular resistance).

In 1998 Koivusalo AM, Schejnin M and Tikkanen I of Finland[16] studied the effect of esmolol on CO2 pneumoperitoneum induced hemodynamic changes in laparoscopic surgeries. In this double blind randomized study esmolol was compared with isotonic saline in 28 patients undergoing laparoscopic surgery in standardized 1 MAC Isoflurane anaesthesia. Alfentanil infusion was used to prevent the increase in Mean Arterial Pressure more than 25% from baseline. They concluded esmolol blunts the pressor response to induction and maintenance of pneumoperitoneum and protect against renal ischemia during pneumoperitoneum.

In 2000, J.L.Joris, J.D. Chiche J L Canivet of Belgium[12] investigated endocrine correlates of the haemodynamic changes induced by the carbon dioxide pneumoperitoneum and the effect of clonidine in modifying these changes. They conducted two studies, each including 20 healthy patients undergoing elective laparoscopic cholecystectomy. In the first study serial measurements of haemodynamics and plasma concentrations of cortisol, catecholamines, vasopressin, rennin, and endothelin were measured at the same time points. In the second study patients were randomly allocated to receive 8 mic./kg. clonidine

infused over 1 hour or placebo before pneumoperitoneum. Haemodynamics and the above
hormones measured similarly.From the observations it was concluded, Vasopressin and catecholamines probably mediate the increase in systemic vascular resistance observed during pneumoperitoneum. Clonidine given before pneumoperitoneum significantly reduced mean arterial pressure, heart rate and the increase in systemic vascular resistance. Clonidine also reduced catecholamine concentrations significantly but did not alter vasopressin and cortisol plasma concentrations.
In 2001 Margarita Coloma, JenW.chiu et al[25], compared esmolol and remifentanyl infusions with respect to their effect on hemodynamic stability and early recovery after outpatient laparoscopic surgery, and concluded that provide haemodynamic stability during desflurane based anesthesia for outpatient gynecological laparoscopic surgery.
In 2002 Dr.Arti Rathore and Dr.H.k.Gupta[3], , studied three doses of esmolol 50mgs, 100mgm, 150mgm in blunting Heart Rate and Blood Pressure response to laryngoscopy and intubation in 100 ASA I Patients undergoing elective surgery under general anaesthesia. They found in their study that all three doses of esmolol effective in blunting heart rate response to intubation, but only 150 mgm esmolol was effective in attenuating the Blood Pressure response to laryngoscopy and intubation.

In2005, Z.Kayhan,D,Aldemir, H.Mutlu and E.Ogus et al[14] have investigated the concentrations of epinephrine, nor epinephrine, vasopressin and angiotensin converting enzyme activity to explore the role of these mediators in the neuro endocrine response to laryngoscopy and tracheal intubation. They studies 100 ASA I patients undergoing elctive surgery. Plasma epinephrine, nor epinephrine, vasopressin and angiotensin converting enzyme concentrations were measured at various time intervals and Blood Pressure and Heart Rate were recorded at corresponding times. They concluded that Blood Pressure, Heart Rate, Plasma Epinephrine, norepinephrine and vasopressin concentrations increased in response to laryngoscopy and intubation, with no change in angiotensin converting enzyme activity in normotensive patients.

In 2005, Maharajan SK et al[23], studied the effect of propranolol on hemodynamic response to airway manipulation and carbon dioxide pneumoperitoneum on patients undergoing laparoscopic cholecystectomy. Sixty three patients undergoing laparoscopic cholecystectomy of ASA physical status I and II were

selected for the study. All patients were premedicated with diazepam 5mg, ranitidine
150mg and metaclopramide 10mg in the night before surgery. They were randomly divided into three groups and were given 1mg propranolol or 0.5mg propranolol or 1 ml of saline. General anesthesia with pethidine, thiopentone, succinylcholine and endotracheal intubation and anesthesia maintained with oxygen, pancuronium and 1+/-0.5% halothane. Heart rate and Blood pressure were recorded at various intervals and recorded. The results were statistically analysed and concluded that 1 mg propranolol is superior to 0.5mg in decreasing haemodynamic response to carbon dioxide pneumoperitoneum in laparoscopic surgeries in ASA I and II patients without significant bradycardia in postoperative period.

# MATERIALS AND METHODS

After obtaining hospital ethical committee approval 60 consenting ASA Class 1 patients , with airway Mallampatti classification 1& 2, in the age group of 15 to 45 undergoing laparoscopic appendicectomy were selected for the study.

**Study design**; prospective randomized double blind controlled study.

Randomization done using a set of computer generated random numbers. The anaesthesia provider and the observer were blinded. Another person other than the anesthesia provider and the observer loaded either inj. Metoprolol or normal saline as per the random numbers and gave it to the anesthesia provider. The syringes were labeled only with the serial no. assigned to the patient

**Preoperative Assessment**:

Thorough pre operative assessment with

medical history,
physical examination and

investigations carried out in all these 60 patients
Hb%,
Total count, differential count
Renal function tests
Blood glucose
Blood grouping
Bleeding time and Clotting time
ECG
Chest X ray.

**Exclusion Criteria**:

1. Hypertension
2. Ischemic heart disease
3. Diabetes mellitus
4. COPD, Bronchial Asthma
5. ECG: rhythm other than sinus, any degree of heart block
6. more than 1 attempt at intubation
7. peripheral vascular disease
8. Patients who were converted to open surgery after laparoscopic visualisation

All the 60 patients were given Tablet Alprazolam 0.25mg, Cap.Omeprazole 20mg, Tablet Ondoncetron 4 mg night before surgery.

On the morning of surgery, while the patient was at rest in the ward Heart Rate and Blood Pressure recorded and these were taken as basal values for the patient.

**Premedication:** For all the patients Inj.glycopyrolate 0.2mg i.m.given 1 hr before surgery.

**Monitors**

In the operation theatre, patients will be connected to

ECG monitor

Non Invasive Blood Pressure Monitor

Pulse oxymeter and

End tidal carbon dioxide

Urine Output were monitored , and all base line values recorded.

In the OT, intravenous access will be established. All the patients will be given a crystalloid fluid bolus of 10 ml/kg. to compensate for overnight starvation and prevent hypotension produced by decreased venous return during

pneumoperitoneum Then maintenance crystaloid fluid will be started at 2ml/kg/hour

Five minutes before induction of anesthesia, the contents of the syringe ( either inj.Metoprolol 50mic.gm/kg diluted to 10 ml or 10ml normal saline) given intravenously over a period of 3 minutes,

**ANESTHESIA**

All the 60 patients received inj.fentanyl 2 micrograms/kg for analgesia and additional 0.5 micrograms /kg every hour for the duration of surgery. They were induced with inj.Propofol 2mg/kg. and inj. Succinylcholine 1.5mg/kg for muscle relaxation, and intubated 60seconds after succinylcholine injection with an appropriate size cuffed endotracheal tube. Intubation was done by the same person in all the cases. Bilateral equal air entry was confirmed. Anesthesia was maintained

with nitrous oxide oxygen mixture 4/2 litres, with isoflurane 1 MAC and Inj.Vecuronium for muscle relaxation.

ET CO2 maintained between 25 to 35 mm of Hg by adjusting the minute ventilation

Intra abdominal pressure maintained at 12 mm of Hg by CO2 insuffolation.

Inj.Neostigmine and inj.glycopyrolate were used for reversal of muscle relaxation. Heart Rate, SpO2, ETCO2 monitored continuously and Blood Pressure(systolic,diastolic,MAP) recorded every 5 minutes, before intubation, one ,five minutes after intubation, before extubation and after extubation and as often required.

Measurements taken at the following timings were noted.

1. Basal
2. One, five minutes after Intubation
3. Before pneumoperitoneum
4. At 15 minutes intervals after establishing pneumoperitoneum
5. Before Extubation and after Extubation

In addition the following things were noted.

1. Duration of the Laryngoscopy
2. Duration of Pneumoperitoneum
3. Episodes of hypertension., were managed with additional inj.Fentanyl 0.25microgram/kg.and the total dose of fentanyl required noted down. If

hypertension persisted, after ruling out hypercarbia it was managed with increasing the isoflurane concentration, and this was noted down.

4. Episodes of hypotension managed by fluid boluses and vasopressors .
5. Hourly Urine output
6. ECG Changes, any Arrhythmias, Bradycardia, whether associated with hypotension
7. Bronchospasm
8. Any other complications, Patients were monitored for 8 hrs post operatively for observation of any side effects.

For the purpose of the study the following definitions were made.

1.Hypertension: increase in MAP more than 25% 0f basal values

2.Hypotension: decrease in MAP more than 25% of basal values

3.Bradycardia: decrease in heart to less than 60/minute.

At the end of the study, using the random numbers chart and the patients serial number, patients were divided into two groups. Patients who received i.v. Metoprolol were put in Metoprolol group (Group M). Patients who received normal saline were put in Control group(Group C).

# OBSERVATIONS AND RESULTS

Metoprolol group(group M) and Control Group(group C) were compared in respect to age , sex, weight, Airway Class, Duration of laryngoscopy, Duration of Pneumoperitoneum and urine output.

There were no episodes of hypoxia in any patient. We were able to maintain $EtCO_2$ within the 25 to 35mm of Hg. Range, in all the patients by adjusting the minute ventilation.

Heart Rate(HR) and Mean Arterial Pressure(MAP) values recorded at one and five minutes after intubation were compared with the basal values of the patient in both the groups. HR and MAP recorded 15 minutes after establishing pneumoperitoneum were compared with Baseline and prepneumoperitoneum values in both the groups. HR and MAP recorded at 15,30,45 minutes after pneumoperitoneum were compared among themselves in both the groups.

In addition Heart rate and Mean Arterial Pressure values recorded after extubation were compared with pre extubation values.

**The following tests were used for statistical analysis**.

1. Two Sample ‘t’ test
2. Mann-Whitney U or Wilcoxon Rank-Sum test for difference in Medians
3. One way analysis of variance(Oneway ANOWA)

P value of less than 0.05 is taken as significant.

## DEMOGRAPHIC PROFILE

### Age(Years)

| Group | Mean | Standard Deviation | Standard Error | P value and Significance |
|---|---|---|---|---|
| Group M | 33.36 | 8.77 | 1.60 | 0.940 |
| Group C | 33.20 | 8.56 | 1-56 | **Not Significant** |

Mean age of the patients in Metoprolol group was 33.36 years, and 33.20 years in Control group. There was no significant difference in age between the two groups.

**Sex**

| Group | Male | Female |
|---|---|---|
| Group M | 12 | 18 |
| Group C | 13 | 17 |

Females were more in both the groups

Females were more in  both the groups

**Weigh(in kilograms)**

| Group | Mean | Standard deviation | Standard error | P Significance |
|---|---|---|---|---|
| Group M | 57.76667 | 9.37 | 1.71 | 0.920 |
| Group C | 57.53 | 8.72 | 1.59 | **Not Significant** |

The Mean weight of the Metoprolol group patients was 57.76 kg, and mean weight of the  Control group patients was57.53 kg.There was no significant difference in weight between the groups.

**Airway**

| Group | MPC 1 | MPC2 |
|---|---|---|
| Group M | 21 | 9 |
| Group C | 22 | 8 |

MPC= Mallampatti Classification

In Metoprolol group 21 patients belong to Mallampatti Airway Class I and 9 belong to Class II. In Control group 22 patients belong to Class I and 8 belong to class II.

**Duration of Laryngoscopy (in seconds)**

| Group | Mean | Standard deviation | Standard error | P Significance |
|---|---|---|---|---|
| Group M | 15.06 | 2.016 | 0.36 | 0.703 |
| Group C | 15.26 | 2.033 | 0.37 | **Not Significant** |

There was no significant difference in duration of laryngoscopy between the two groups.

**Duration of pneumoperitoneum(in minutes)**

| Group | Mean | Standard deviation | Standard error | P Significance |
|---|---|---|---|---|
| Group M | 84.26 | 18.91 | 3.45 | 0.934 |
| Group C | 83.86 | 18.57 | 3.39 | **Not Significant** |

There was no significant difference in the duration of pneumoperitoneum between the two groups

**Urine Output at 1 hour after induction(in milliliters)**

| Group | Mean | Standard deviation | Standard error | P Significance |
|---|---|---|---|---|
| Group M | 110.33 | 12.99 | 2.37 | <0.01 |
| Group C | 90.83 | 9.74 | 1.77 | **Significant** |

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The Mean Urine Output at 1 hour after induction of anaesthesia was110.33 ml in Metoprolol group and 90.83 ml in Control group. There was significantly more urine output in the Metoprolol group than the control group at 1 hour after induction of anesthesia.

During the 8 hour post operative period The Mean Per hour Urine Output in the Metoprolol group was108.5ml/hour, in the control group it was 105 ml. All the patients in both the groups had more than 0.5ml/kg. urine output during the post operative period.

**Heart rate and Blood Pressure response to intubation 1 and 5 minutes after intubation compared with baseline Heart rate in both groups**.

**Group M**

| Time | Mean | Standard deviation | Standard error | P Significance |
|---|---|---|---|---|
| Basal HR | 81.5 | 7.65 | 1.39 | |
| HR 1 minuteafter Intubation | 81.16 | 7.87 | 1.43 | 0.86 **Not Significant** |
| HR 5 Minutes after intubation | 81.46 | 7.04 | 1.28 | 0.98 **Not significant** |
| Basal MAP | 93.96 | 2.76 | 0.50 | |
| MAP 1 minute after intubation | 91.46 | 3.98 | 0.72 | 0.006 **Significant decrease** |
| MAP 5 minutes after intubation | 91.96 | 4.99 | 0.91 | 0.06 **Not Significant** |

**Group C**

| Time | Mean | Standard deviation | Standard error | P Significance |
|---|---|---|---|---|
| Basal HR | 82.83 | 8.62 | 1.57 | |
| HR 1 minuteafter Intubation | 86.13 | 9.51 | 1.73 | 0.16 **Not significant** |
| HR 5 Minutes after intubation | 85.93 | 8.37 | 1.52 | 0.16 **Not significant** |
| Basal MAP | 93.76 | 3.18 | 0.58 | |
| MAP 1 minute after intubation | 98.46 | 7.31 | 1.33 | 0.018 **Significant** |
| MAP 5 minutes after intubation | 99.76 | 7.99 | 1.45 | 0.018 **Significant** |

**Heart rate and Blood Pressure response to intubation**

**Group M**

1min= 1 minute after intubation 5 min.=5 minutes after intubation
HR=Heart Rate MAP= Mean Arterial Pressure

In the Metoprolol group there was no significant difference in Heart rate from base line in both I minute and 5 minutes after intubation. There was no significant difference in MAP 5 minutes after intubation from baseline MAP. There was a small but significant decrease in MAP 1 minute after intubation from baseline Mean Arterial Pressure.

**Heart rate and Blood Pressure response to intubation**

**Group C**

1min= 1 minute after intubation 5 min.=5 minutes after intubation
HR=Heart Rate MAP= Mean Arterial Pressure

In the control group, there was no significant increase in Heart rate from Basal Heart rate in both one and five minutes after intubation. But there was a significant increase in Mean Arterial Pressure from Basal values during both 1minute and 5 minutes after intubation.

**Heart Rate and Mean Arterial Pressure readings measured at 15 minutes after establishing pneumoperitoneum** were compared with basal and prepneumoperitoneum readings in both the groups.

**Group** M

| Time | Mean | Standard deviation | Standard error | P Significance |
|---|---|---|---|---|
| Basal HR | 81.5 | 7.65 | 1.39 | 0.86 |
| HR 15 minutes after PNP | 81.83 | 7.26 | 1-32 | **Not Significant** |
| Basal MAP | 93.96 | 2.76 | 0.50 | 0.88 |
| MAP 15 minutes after PNP | 94.2 | 8.43 | 1.54 | **Not Significant** |
| HR Before PNP | 80.23 | 6.81 | 1.24 | 0.38 |
| HR 15 Minutes after PNP | 81.83 | 7.26 | 1.32 | **Not Significant** |
| MAP Before PNP | 93.06 | 5.63 | 1.02 | 0.54 |
| MAP 15 minutes after PNP | 94.2 | 8.43 | 1.54 | **Not Significant** |

HR=Heart Rate MAP=Mean Arterial Pressure
PNP=Pneumoperitoneum

**HR and BP response to Pneumoperitoneum**:

**Group M**

HR=Heart Rate MAP=Mean Arterial Pressure
15 min.=15 minutes after pneumoperitoneum(PNP)

**Group C**

| Time | Mean | Standard deviation | Standard error | P Significance |
|---|---|---|---|---|
| Basal HR | 82.83 | 8.62 | 1.57 | 0.02 |
| HR 15 minutes after PNP | 88.53 | 10.79 | 1.97 | **Significant** |
| Basal MAP | 93.76 | 3.18 | 0.58 | <0.01 |
| MAP 15 minutes after PNP | 104.63 | 13.75 | 2.51 | **Significant** |
| HR Before PNP | 77.9 | 6.65 | 1.21 | <0.01 |
| HR 15 Minutes after PNP | 88.53 | 10.79 | 1.97 | **Significant** |
| MAP Before PNP | 91.03 | 4.77 | 0.87 | <0.01 **Significant** |
| MAP 15 minutes after PNP | 104.63 | 13.75 | 2.51 | |

HR=Heart Rate MAP=Mean Arterial Pressure PNP=Pneumoperitoneum

**HR and BP response to Pneumoperitoneum**:

**Group C**

HR=Heart Rate MAP=Mean Arterial Pressure
Before=Before establishing pneumoperitoneum

15min.=15minutes after establishing pneumoperitoneum

15 minutes after establishing pneumoperitoneum,In Metoprolol group there was no significant increase in Heart Rate and Mean arterial Pressure either from Basal or Pre Pneumoperitoneum recordings. In Control group there was significant increase in both Heart rate and Mean Arterial Pressure from Basal and Pre Pneumoperitoneum recordings.

**Heart Rate and Mean Arterial Pressure recorded at 15,30,45** minutes after establishing pneumoperitoneum were compared among themselves for any significant increase or decrease in both the groups.

**GroupM**

| Variable | Time | Mean | Standard deviation | Standard error | P Significance |
|---|---|---|---|---|---|
| Heart Rate | 15 min.after PNP | 81.83 | 7.26 | 1.32 | 0.858 **Not Significant** |
| | 30 min.after PNP | 82.63 | 7.28 | 1.33 | |
| | 45 min.after PNP | 82.83 | 7.59 | 1.38 | |
| Mean Arterial Pressure | 15 min.after PNP | 94.20 | 8.43 | 1.54 | 0.98 **Not Significant** |
| | 30 min.after PNP | 94.03 | 3.90 | 0.71 | |
| | 45 min.after PNP | 94.33 | 3.76 | 0.68 | |

**Group C**

| Variable | Time | Mean | Standard deviation | Standard error | P Significance |
|---|---|---|---|---|---|
| Heart Rate | 15 min.after PNP | 88.53 | 10.79 | 1.97 | 0.86 **Not Significant** |
| | 30 min.after PNP | 87.4 | 8.99 | 1.64 | |
| | 45 min.after PNP | 88.6 | 8.70 | 1.58 | |
| Mean Arterial Pressure | 15 min.after PNP | 104.63 | 13.75 | 2.51 | 0.571 **Not Significant** |
| | 30 min.after PNP | 103.03 | 10.17 | 1.85 | |
| | 45 min.after PNP | 101.66 | 7.70 | 1.40 | |

HR=Heart Rate PNP=Pneumoperitoneum

MAP=Mean Arterial Pressure PNP=Pneumoperitoneum

There was no significant difference in the Heart Rate and Mean Arterial Pressure between the recordings taken after 15,30,45 minutes after establishing pneumoperitoneum in both the groups.

**Heart Rate and Mean Arterial Pressure after extubation were compared with pre extubation measurements** in both the groups

**Group M.**

| Group | Time | Mean | Standard deviation | Standard error | P Significance |
|---|---|---|---|---|---|
| GroupM | Before Extubation HR | 83.73 | 6.84 | 1.25 | 0.30 **Not** |
| | After ExtubationHR | 85.86 | 9.03 | 1.64 | **Significant** |
| | Before Extubation MAP | 95.16 | 3.59 | 0.65 | 0.10 **Not Significant** |
| | After Extubation MAP | 96.76 | 3.97 | 0.72 | |

BE=Before Extubation AE=After Extubation
HR=Heart Rate MAP=Mean Arterial Pressure

**Group C**

| Group | Time | Mean | Standard | Standard error | P |
|---|---|---|---|---|---|

| | | | deviation | | Significance |
|---|---|---|---|---|---|
| Group C | Before Extubation HR | 86.33 | 6.79 | 1.24 | <0.01 **Significant** |
| | After ExtubationHR | 96.73 | 9.93 | 1.81 | |
| | Before Extubation MAP | 100.83 | 6.67 | 1.21 | <0.01 **Significant** |
| | After Extubation MAP | 108.96 | 8.93 | 1.63 | |

BE=Before Extubation AE=After Extubation HR=Heart Rate
MAP=Mean Arterial Pressure

In Metoprolol group, there was no significant difference in Heart Rate and Mean Arterial Pressure between before extubation and after extubation measurements. In Control group there was significant increase in Heart Rate and Mean Arterial Pressure after extubation compared to the pre extubation values.

**COMPARISON OF INTRAOPERATIVE EVENTS**

| S.No | Event | Incidence in Group M | Incidence in Group C |
|---|---|---|---|
| 1 | Hypertensive episodes | 2 | 10 |
| 2 | Additional Fentanyl requirements | 2 | 10 |
| 3 | Increased MAC requirements | 0 | 5 |
| 4 | Hypotensive episodes | 1 | 2 |

| | | | |
|---|---|---|---|
| 5 | Fluid Bolus requirement | 1 | 2 |
| 6 | Vasopressor requirement | 0 | 0 |
| 7 | Bradycardia | 2 | 2 |
| 8 | ECG Changes | 2(Sinus Bradycardia) | 2(sinus Bradycardia) |
| 9 | Bronchospasm | 0 | 0 |

**Post Operative Events**

| S.No | Event | Incidence in Group M | Incidence in Group C |
|---|---|---|---|
| 1 | Bradycardia | 0 | 0 |
| 2 | ECG Changes | 0 | 0 |
| 3 | Bronchospasm | 0 | 0 |
| 4 | Postoperative Nausea and vomiting | 3 | 4 |

**Comparison of Perioperative events**

PONV= Post Operative Nausea and Vomiting

# DISCUSSION

Stress response due to sympathetic stimulation during laryngoscopy and tracheal intubation produces,

Hypertension
Tachycardia and
Tachyarrhythmias

These reflexes can be decreased by pretreatment with lignocaine intravenous or topical, narcotics or ß blockers, ensuring adequate depth of anesthesia at the time of laryngoscopy and short duration of laryngoscopy.

Haemodynamic repercussions of Pneumoperitoneum are

Elevations of arterial pressure
Increase in Heart rate
Increase of systemic and pulmonary vascular resistance
Decreased cardiac output

Decrease in cardiac output is due to decrease in venous return with increase in intra abdominal pressure. This can be attenuated by increasing circulatory volume before pneumoperitoneum by fluid loading or tilting the table to a slight head down position before pneumoperitoneum.

Increase in Systemic Vascular Resistance(SVR), Blood Pressure, Heart Rate(HR) is considered to be mediated by mechanical as well as neurohumeral factors[41]. Mechanical stimulation of peritoneal receptors also result in increased vasopressin release[21]. Release of catecholamines and activation of rennin angiotensin system during pneumoperitoneum produce the hemodynamic changes associated with pneumoperitoneum[8,42].Absorbed carbon dioxide leading to hypercarbia will produce sympathetic stimulation and increase in heart rate and blood pressure.

Metoprolol, a selective $ß_1$ adrenergic blocking agent acts by

Competitive antagonism of catecholamines at peripheral(especially cardiac) adrenergic neuron sites;
A central effect leading to reduced sympathetic outflow to the periphery;
Suppression of rennin activity.

These properties of metoprolol make it a candidate for suppressing the stress response. Moreover, the elimination halftime of Metoprolol being 3.5 hours allows it to be administered as a single dose covering the duration of surgery. Thus in this study we have evaluated the efficacy of injection metoprolol 50 micrograms/kg. i.v., in attenuating these stress responses.

We hypothesized that inj.Metoprolol 50mic.gms/kg.i.v. given 5 minutes before induction of anesthesia will attenuate these stress responses during laparoscopic surgeries and it may cause bradycardia, Atrio Ventricular dissociation, congestive cardiac failure, bronchospasm and nausea and vomiting. With the observations made we tested this hypothesis statistically and compared the results with a control group where metoprolol is not given.

**DEMOGRAPHIC PROFILE**

Both Metoprolol group(group M) and control group(group C) were similar in respect to age, sex and weight distribution.

There was no significant difference in duration of laryngoscopy and duration of pneumoperitoneum between the two groups.

**HEMODYNAMIC RESPONSE TO INTUBATION**

There was no significant difference in heart rate at 1 and 5 minutes after intubation compared to basal heart rate in both the groups. It may be that, our anesthetic technique and short duration of laryngoscopy effectively prevented increase in heart rate. However there was significant increase in Mean Arterial Pressure(MAP), at 1 and 5 minutes after intubation compared to basal MAP in control group. But in Metoprolol group compared to the basal MAP at 1 minute

after intubation there was a small but significant decrease in MAP,5 minutes after intubation there was no significant difference in MAP. From these observations Metoprolol seems to be effective in attenuating the stress response to intubation.

These observations are similar to the findings of **Kumar M;Tikkle AC et al**[17], who studied the effect of inj.Metoprolol,i.v.3mgm. given 5 minutes before induction of anesthesia and concluded Metoprolol effectively attenuated the cardiovascular response to laryngoscopy and intubation

These observations also correlate with the study of **J.Manusson,M.D.,T.Thulin,O.Werner et al of sweden**[22], who studies the effect of pretreatment with Metoprolol in patients undergoing surgery and concluded metoprolol significantly reduced arterial pressure both during undisturbed anesthesia and during intubation and extubation.

Results of this study indicate Metoprolol's efficacy in attenuating the stress response to intubation is comparable to Nitroglycerin , demonstrated by Mikawa K, Hasegawa M, Suzuki T, Obara H et al[29].

Results of this study regarding the efficacy of Metoprolol in attenuating the stress response to intubation , is comparable to that of propronolol demonstrated by **Maharajan et al**[23].Metoprolol's efficacy is also comparable with esmolol's efficacy demonstrated by**Arthi Rathore,Dr.H.K.Guptha et al**[14].

**Hemodynamic response during $co_2$ pneumoperitoneum**

There was a significant increase in Heart Rate and Mean Arterial pressure in Control group 15 minutes after pneumoperitoneum compared to both basal and pre pneumoperitoneum values. But in Metoprolol group there was no significant difference in Heart Rate and Mean Arterial Pressure compared to basal and pre pneumoperitoneum values. From the observations it seems, Metoprolol is effective in attenuating the stress response induced by pneumoperitoneum.

In attenuating the stress response to pneumoperitoneum results with metoprolol in this study are comparable with

1. **Propronolol**, Maharajan SK et al[23],who demonstrated propranolol is effective in decreasing the stress response due to airway manipulation and $CO_2$ pneumoperitoneum in patients undergoing laparoscopic surgeries.
2. **Esmolol,** Koivusalo AM,Schejnin M, Tikkannen I et al[16] who demonstrated that esmolol blunts the pressor response

to induction and maintenance of pneumoperitoneum and may protect against renal ischemia.

3.

4. **Clonidine**,JL Jnis,JD Chiche et al[12], who found that clonidine is effective in attenuating the stress response to pneumoperitoneum.

**Lamintaustra R, Syvalathi E et al[19]**, studied the effect of ß blockers on plasma rennin activity, in an exercise test and demonstrated exercise induced increase in plasma rennin activity can be inhibited by $ß_1$ adrenergic blockers.

In this study, 1 hour after induction of anesthesia, there was significantly more urine output in Metoprolol group compared to the Control group. Suppression of increase in rennin activity induced by pneumoperitoneum by Metoprolol is the likely mechanism for this observation. This also corelates with the observations of , **Koivusalo AM,Schejnin M, Tikkannen I et al[16]** , who demonstrated that esmolol blunts the pressor response to induction and maintenance of pneumoperitoneum and may protect against renal ischemia.

**RESPONSE TO EXTUBATION**

In the Metoprolol group there was no significant difference in Heart rate and Mean Arterial Pressure measured before and after extubation. But in Control group, there was a significant increase in both HR and MAP compared to

the pre extubation values. Our observations also correlate with the study of **J.Manusson,M.D.,T.Thulin,O.Werner et al** of sweden[22]. The results are also comparable to that of propronolol in the study of **Maharajan SK et al[23].**

**PERIOPERATIVE EVENTS**

All the patients were monitored intraoperatively and 8 hours post operatively for any complications, and the following observations made.

**Intraoperative:**

| S.No | Event | Incidence in Group M | Incidence in Group C |
|---|---|---|---|
| 1 | Hypertensive episodes | 2 | 10 |
| 2 | Additional Fentanyl requirements | 2 | 10 |
| 3 | Increased MAC requirements | 0 | 5 |
| 4 | Hypotensive episodes | 1 | 2 |
| 5 | Fluid Bolus requirement | 1 | 2 |
| 6 | Vasopressor requirement | 0 | 0 |
| 7 | Bradycardia | 2 | 2 |
| 8 | ECG Changes | 2(Sinus Bradycardia) | 2(sinus Bradycardia) |
| 9 | Bronchospasm | 0 | 0 |

**Hypertensive Episodes**:

Highest Mean Arterial Pressure observed in Metoprolol group was 126mm of Hg,in Control group it was 134 mm of Hg. Both occurred during the first 15 minutes of $CO_2$ pneumoperitoneum.

In Metoprolol group 2 patients developed hypertensive episodes, they were managed with supplementing additional fentanyl. In control group 10 patients had hypertensive episodes, all of them were given additional fentanyl; Five among

them required increase in Isoflurane concentration to control blood pressure. It is clear that opioid requirement and Isoflurane requirement are more in the Control group compared to the Metoprolol group.

**Hypotensive Episodes**:

One patient in Metoprolol group and two patients in control group developed hypotensive episodes. Lowest Mean arterial pressure was 62 mm of Hg. In Metoprolol group and 65 mm of Hg. In Control group. All of them responded to fluid bolus and none of them required any vasopressor.

**Others:**

2 patients in each group developed sinus bradycardia. Only one patient in the Metoprolol group developed a heart rate less than fifty(47), it responded promptly to inj. Atropine 0.6mg i.v.. Other three patients who developed brady cardia had heart rates between 50 and 60, not associated with any hypotension and they did not require any treatment. There were no other ECG abnormalities or bronchospasm in any of the patients in both the groups.

**Post Operative Events**

| S.No | Event | Incidence in Group M | Incidence in Group C |
|---|---|---|---|
| 1 | Bradycardia | 0 | 0 |
| 2 | ECG Changes | 0 | 0 |
| 3 | Bronchospasm | 0 | 0 |
| 4 | Postoperative Nausea and vomiting | 3 | 4 |

There were no significant complications during the 8 hours post operatively in both group of patients, other than post operative nausea and vomiting. Three patients in the Metoprolol group and four patients in the Control group had post operative nausea and vomiting, all of them occurred during the first hour post operatively. There was no significant difference in the average hourly urine output between the two groups.

In this study there was no significant difference in the incidence of complications between the Metoprolol group and the Control group.

# SUMMARY

Aim of this study is to evaluate the efficacy of inj.Metoprolol 50 mic.gms/kg. i.v. given 5 minutes before induction of anesthesia in attenuating the hemodynamic response to intubation and carbon dioxide pneumoperitoneum and to look for any adverse effects.

There was no significant difference between the Metoprolol group and Control group in respect to age, sex distribution, weight, Airway class, duration of laryngoscopy and pneumoperitoneum.

After 1 and 5 minutes after intubation, there was no significant increase in heart rate compared to basal heart rate in both the group. Our anesthetic technique was sufficient to blunt the heart rate response to intubation in the control group. But there was significant increase in Mean Arterial Pressure in Control group from basal readings during both 1 and 5 minutes after intubation. In Metoprolol group there was a small but significant decrease in Mean Arterial Pressure 1 minute after intubation, and no significant change 5 minutes after intubation.

During $CO_2$ Pneumoperitoneum there was a significant increase in Heart Rate and Mean Arterial pressure in Control group 15 minutes after pneumoperitoneum compared to both basal and pre pneumoperitoneum values. But in Metoprolol group there was no significant difference in Heart Rate and Mean Arterial Pressure compared to basal and pre pneumoperitoneum values. There was no significant difference in Heart Rate and Mean Arterial Pressure recordings at 15,30,45 minutes after pneumoperitoneum in both the groups.

Similarly, there was a significant increase in Heart Rate and Mean Arterial Pressure in Control group after extubation compared to the pre extubation readings. But there was no significant difference in Heart Rate and Mean Arterial Pressure between pre extubation and after extubation recordings in Metoprolol group. Moreover, there was significantly more urine output after 1 hour of induction of anesthesia in Metoprolol group compared to Control group.

In Metoprolol group two patients had hypertensive episodes and they were controlled with additional fentanyl supplementation. In Control group ten patients developed hypertensive episodes all of them were given additional fentanyl. In

addition to fentanyl 5 of them required additional increase in Isoflurane inspired concentrations to control the increase in blood pressure. One patient in the

Metoprolol group and two in the Control group had hypotensive episodes, and they were managed with fluid boluses. None required vasopressors. Two patients in both the groups developed sinus bradycardia, Three of them did not require any treatment, one in the Metoprolol group was treated with inj. Atropine 0.6mg i.v. Three patients in Metoprolol group and four patients in Control group had mild postoperative nausea and vomiting.

Many studies have demonstrated similar efficacy with other ß blockers like propranolol and esmolol,Metoprolol scores over propranolol in being cardioselective so that it can be used in situations where propranolol is contra indicated. The disadvantage with esmolol is, it has to be repeated or an infusion has to be maintained because of its ultra short duration of action, whereas a single dose of Metoprolol is effective for the entire duration of surgery.

# CONCLUSION

1. Inj.Metoprolol 5µgm./kg. i.v. given 5 minutes before induction of anesthesia effectively attenuates the hemodynamic response to laryngoscopy, intubation and carbon dioxide pneumoperitoneum
2. There were no significant complications associated with inj.Metoprolol 50µgm./kg/i.v during intraoperative period and 8 hours postoperatively.

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PROFORMA

Name :

Age : Sex: Weight:

Serial No:

ASA Status: Airway: MPC

| Time | Heart Rate | BP Systolic/diastolic(MAP) | ETCO2 | SpO2 |
|---|---|---|---|---|
| Basal | | | | |
| 1 minute after intubation | | | | |
| 5 minutes after intubation | | | | |
| Before pneumoperitoneum(PNP) | | | | |
| 15 minutes after PNP | | | | |
| 30 min after PNP | | | | |
| 45 min after PNP | | | | |
| Before extubation | | | | |
| After extubation | | | | |

Duration of laryngoscopy :

Duration of surgery :

Episodes of Hypertension :

Timing :
Managed with :

Episodes of Hypotension :

Timing :
Managed with :

Other complications :

Hourly urine output :

Bradycardia: lowest HR: Managed with( total dose required)

ECG changes:

Bronchospasm;

Any other com plications:

Intraoperatively:

Postoperatively